

EXHIBIT AV

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MBBS, PhD, FRACP
Genetic Cardiologist
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I agree to be bound by Regulation 31.27 Uniform Civil Procedure Rules 2005 and the expert witness code of conduct.

I am a Cardiologist, and have completed 5 years of clinical and research fellowship in inherited cardiac conditions. I have a PhD in Long QT Syndrome. I work as a Genetic Cardiologist at Flinders Medical Centre in South Australia. My clinical expertise includes conditions such as long QT syndrome, Brugada syndrome, Catecholaminergic polymorphic ventricular tachycardia, hypertrophic cardiomyopathy, familial dilated cardiomyopathy and arrhythmogenic cardiomyopathy amongst others. I have experience assessing cases of sudden unexpected death which involves reviewing: the deceased's personal history, the circumstances of death, family history of sudden death/inherited cardiac conditions, investigations available from life of the deceased, organizing and interpreting investigations in living relatives, ordering a "molecular autopsy" ie. genetic studies in the deceased, considering genetic testing in living relatives. I am the co-author of the Cardiac Society Australia and New Zealand document "Update on the diagnosis and management of familial long QT syndrome".(1)

In response to your questions:

1) What categories, if any, are used to identify the impact of genetic variants on cardiac health?

Commonly, and formerly, the terms "mutation" (a permanent change in the DNA sequence) and "polymorphism" (a variant with a frequency above 1%) have been associated with being pathogenic (disease causing) and benign (not disease causing) respectively.(2)

There is in fact, a gradient between one extreme and the other. Consequently, the American College of Medical Genetics and Genomics recommend that the term "variant" is used and qualified by 5 descriptive classes: "pathogenic" (class 5), "likely pathogenic" (class 4), "uncertain significance" (class 3), "likely benign" (class 2) or "benign" (class 1). They propose that "likely" be reserved to cases when over 90% certainty exists for being either disease causing or not. Each laboratory uses a combination of population, computational/predictive, functional, segregation, de novo, allelic and other data to interpret and classify sequence variants.(2)

In practice then, only class 5 variants are used with very high levels of confidence: if a class 5 variant is found, we can quite confidently say that that genetic variation has caused disease. The confidence with which class 4 variants are used varies according to the weight of evidence in that particular case, and therefore probably between institutions. Class 1 and 2 variants are often not reported by laboratories as they are not believed to be involved in causing disease. Class 3 is the middle ground, "genetic purgatory"(3), where a genetic variation has been found, but it's role in causing disease is not yet known.

As more is learnt about the genetics of inherited cardiac conditions,(4) genetic variants are reclassified (particularly class 3), so that one which may not be associated with disease now, may be proven to be associated with disease in the future, and vice versa.(4, 5)

- 2) **When you are considering the cardiac functioning of a child, do you consider the impact of genetic variants?**
- 3) **What emphasis do you place on genetic variants when considering the cardiac health of a child?**

This depends on the particular situation, and of course, this answer is limited to discussing genetic variants associated with inherited cardiac conditions. I have chosen to answer these two questions together.

Health impact when a relative has an inherited cardiac condition:

The simplest situation would be when assessing the relative of an affected patient and where that patient carries a disease causing variant. This is called cascade testing. To understand cascade testing, it is important to know that inherited cardiac conditions are usually inherited in an autosomal dominant fashion.(6) That is, an affected individual has a 50% chance of passing the condition on to each child, each of their siblings has 50% chance of being affected, and that it was inherited from one of their parents. Therefore, when a diagnosis is made, each first degree relative has a 50% chance of carrying the genetic variant, whether or not that variant is found on genetic testing. Traditionally, and where genetic testing is unavailable or not possible, those relatives should then undergo clinical screening with cardiac investigations to determine whether they are also at risk, even though they may not have yet manifested the disease, i.e. they are “pre-symptomatic”.

Cascade testing is cheaper(7) and more definitive than clinical testing in the case of a class 5 (or potentially class 4) variant. In this situation, knowing whether the child has inherited the disease causing variant may have a significant impact on considering their health and risk of cardiac event.(8) If they have inherited the variant, they are at risk of syncope and sudden cardiac death, and risk reducing therapies can be instituted or surveillance programs can be commenced (depending on the disease) with the aim of preventing sudden unexpected death, regardless of whether they have clinical signs of disease.(4) If they have not inherited the variant, they are generally informed that they are not at risk, cannot pass the condition on to their children and are discharged from follow-up.

Impact when investigating the proband: diagnosis

A more complex situation arises when assessing a patient suspected of having an inherited cardiac condition such as when they have presented with an abnormal ECG, or symptoms such as syncope or resuscitated cardiac arrest. In this situation, the first assessment is usually a clinical one.(9) This comprises a personal history of the patient, including such factors such as previous “blackouts” or “seizures” (inherited cardiac conditions are often misdiagnosed as seizure disorders)(10), a physical examination and a review of any investigations they have previously had (such as ECGs or cardiac imaging). A (minimum) three generation family tree should be constructed, looking particularly for history of sudden unexpected death, including unexplained motor vehicle accidents and unexplained (near) drownings which may have resulted from sudden cardiac death, amongst other features. Autopsy reports are examined, firstly to ensure they contain sufficient detail. They may provide a cause of sudden death, such as ischaemic heart disease or an inherited condition such as hypertrophic cardiomyopathy. Review by a cardiac pathologist is ideal in the first instance, and may be required to review the case if the diagnosis is equivocal.

Cardiac investigations in the individual, and in the individuals parents, siblings and children should be performed as indicated. This usually includes at least one 12-lead ECG, an echocardiogram (ultrasound of the heart) and an exercise stress test.

Having gathered all this information, a clinical decision as to whether the person was “probably”, “possibly” or “unlikely” to be affected by a cardiac inherited condition would be made. This can be objectified by the use of clinical scores such as the Schwartz score,(11) or by following diagnostic criterion.(12, 13) This is called “determining the phenotype” of the patient, and this clinical judgement, is a vital part of determining whether someone is affected by an inherited cardiac condition.

This is usually followed by genetic testing, usually a “panel” of genes known to be associated with the suspected condition. The genetic testing is performed in the knowledge of its limitations: science does not yet know all the genetic variants that cause inherited cardiac conditions. In the best case scenario, when an individual definitely has unequivocal long QT syndrome, the pick-up rate of genetic testing is approximately 75-80%.(14) In other conditions, the pick-up rate is much lower, for example 30% in dilated cardiomyopathy, and is unknown and likely much lower, in other conditions.(14) Therefore, genetic tests are not used to “rule out” disease, only to confirm its presence, to assist with cascade testing as previously described, to confirm or increase precision of diagnosis and to help guide or increase precision of risk stratification and treatment (see below).

Impact: confirming diagnosis and consequent change in management

In a minority of cases genetic testing is to help confirm a diagnosis if it was uncertain in the proband (the first person being assessed clinically). As above, a “negative” (ie class 1-3 variant) genetic test in these settings would never exclude a diagnosis, only confirm it if a positive result was obtained. In this situation of a “negative” result, ie a class 1-3 variant, the genetic results would be labelled “uninformative”. Confirming a diagnosis can have important implications for management of disease and identifying at risk relatives.(4, 14)

Furthermore, a positive genetic test result can diagnose the condition in an asymptomatic individual, or one who does not clinically manifest the disease. Again, this can have an immediate effect on management of the individual; for example in the case of catecholaminergic polymorphic ventricular tachycardia being diagnosed through cascade genetic testing in an asymptomatic relative, treatment with the aim of reducing the risk of death is recommended.(15) In the case of being genotype positive for an inherited cardiomyopathy, surveillance would be recommended to detect signs of disease and/or high risk features.(13)

Impact: increasing precision of diagnosis and consequent change in management

In particular situations, the genetic results can increase the precision of diagnosis, in turn helping determine prognosis and guide therapeutic options. If a disease causing variant is identified in gene associated with an inherited arrhythmia syndrome, risk reducing therapy would be considered and likely instituted, even in a child without clinical signs of disease. In long QT syndrome, knowing the gene involved (and therefore the “type” of long QT syndrome) has significant impact on identifying and reducing risk. Those affected by disease causing variants in the long QT type 1 gene, *KCNQ1*, are more likely to have cardiac events whilst swimming, and boys between the age of 5-15 are at higher risk of events. The risk of sudden death in these individuals is also significantly reduced by taking a beta-blocker tablet. This compares to long QT type 2 (*KCNH2*) where those at highest risk are women, particularly in the first nine months after giving birth, and when startled by something such

as an alarm clock or phone ringing during the night.(9, 16-18) Those with familial dilated cardiomyopathy carrying a *LMNA* disease causing variant have a more severe course of disease with higher rates of cardiac events including sudden death.(19) In these patients, when other risk factors are also present, a prophylactic implantable cardioverter defibrillator may be recommended.(15, 19)

Impact: increase precision of prognostication

Usually after a diagnosis is made (either clinically or genetically), risk stratification of the patient is performed. That is, where available clinical and genetic factors are used to determine the patient's prognosis i.e. their risk of life-threatening heart arrhythmias and sudden cardiac death.(15) For example, if two disease causing variants are identified, or if a particularly high risk variant is identified, this may mean risk-reducing therapies need to be more aggressively pursued.(15, 20)

4) At what age is ECG reliable in young children?

I am an adult cardiologist, but gained experience interpreting paediatric ECGs in relation to inherited cardiac conditions during my four years working at Starship Children's Hospital in New Zealand. I lack the extensive experience of a full time paediatric cardiologist in this area, and therefore in equivocal or difficult situations, I would seek their advice and guidance. Having said that, significant changes occur in the heart in the first month of extra-uterine life, and given this, I would prefer to defer ECG assessment until at least 4 weeks of age, and preferably 6-8 weeks.(21, 22)

5) At what age is it usual to employ genetic testing on a child (in a current clinical context)?

It is possible to perform genetic testing at any age, and can be recommended from birth.(14) In the case of the inherited arrhythmia syndromes such as long QT syndrome, catecholaminergic polymorphic ventricular tachycardia and Brugada syndrome, it is appropriate to perform genetic testing as soon as possible. This is because there are interventions and/or life style modifications available which can reduce the risk of sudden death as discussed previously.(14)

In the case of inherited cardiomyopathies such as hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathy or familial dilated cardiomyopathy it is possible to perform genetic testing, and international guidelines would support this because children are still at risk.(14)

Others consider it is more appropriate to wait until the child is old enough to participate in the consent process themselves,(23) particularly when management may not be affected by the results before the child reaches age of consent.

6) Any further comments you wish to make

References

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- of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2015;17(5):405-24.
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Dr Kathryn Ellen Waddell-Smith

MBBS (2004)

PhD (2018)

FRACP, Adult Cardiology (2012)

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CLINICAL EXPERIENCE

Cardiologist	Heart and Vascular	2019
Mentor, Reflective Professionalism Program	Flinders University, Australia	2019
Genetic Cardiologist	Flinders Medical Centre	2018 – Current
Introduction to Clinical Skills Coordinator	Flinders University, Australia	2018
Cardiology Salaried Medical Officer	Flinders Private Hospital, Australia	2018 – Current 2012 – 2013
Senior Clinical Fellow in Inherited Cardiac Conditions	Addenbrooke's and Papworth Hospitals, Cambridge, United Kingdom	2017 – 2018
National Heart Foundation and Green Lane Research and Educational Fund Fellow in Cardiac Inherited Disease	Starship Children's and Auckland City Hospitals, Auckland District Health Board, New Zealand	2013 – 2017
Senior Fellow and Research Fellow, Advanced Cardiology Trainee	Flinders Medical Centre, Australia	2010 - 2013
Basic Physician Trainee	Royal Adelaide Hospital, Australia	2007 – 2009
Resident Medical Officer	Royal Adelaide Hospital, Australia	2006
Intern	Royal Adelaide Hospital, Australia	2005

I am a Consultant Genetic Cardiologist practicing at Flinders Medical Centre, and work in the private sector as a General Cardiologist. My particular expertise in inherited cardiac conditions was gained during five years of clinical and research fellowships where I was the inaugural fellow in Inherited Cardiac Conditions in both Auckland New Zealand and Cambridge United Kingdom.

From 2013 - 2017, I worked at Auckland District Health Board under the primary supervision of Professor Jon Skinner seeing adult and paediatric patients affected, or potentially affected, by inherited cardiac conditions. I was involved in clinical and diagnostic assessment, ongoing management of patients, and clinical and genetic screening of their relatives, including relatives of the suddenly deceased. Our multidisciplinary team comprising adult and paediatric cardiologists, geneticists, a molecular geneticist, genetic counselors and a pathologist discussed clinical and genetic results and formulated management plans. We also reviewed cases of sudden unexpected death in the young referred by the Coronial Services, organizing molecular autopsy in the deceased, and genetic and clinical testing in relatives as appropriate.

At Cambridge University (Addenbrooke's) and Papworth Hospitals, United Kingdom I expanded my experience to include Familial Hypercholesterolaemia, Aortopathies, vascular manifestations of connective tissue diseases, Fabry's Disease, Cardiac Vasculitis and general cardiology including coronary care. I worked within a multidisciplinary team of physicians, cardiologists, electrophysiologists, surgeons, dermatologists, geneticists and genetic counselors, regularly participating in various multidisciplinary team meetings.

My expertise encompasses channelopathies, familial cardiomyopathies, aortopathies, hypercholesterolaemia and young sudden death in addition to Fabry's disease and cardiac vasculitis. Multi-disciplinary teamwork is imperative in the field.

A list of my publications follows. During this time, I supervised medical students in data collection and basic interpretation, and worked closely with other researchers and statisticians.

My research goal is to prevent sudden cardiac death in the young through gene discovery and enhancing clinical understanding of these conditions. The academic component of my first fellowship was encapsulated in a PhD through The University of Auckland: "Identifying and Reducing Risk in Familial Long QT Syndrome", which was awarded in 2018. I have experience supervising students in data collection and basic data interpretation, and of working closely with other researchers and statisticians. In addition to developing research locally at Flinders Medical Centre, I am currently involved in the Australian Cardiovascular Genetics Flagship. Furthermore, I am the Chair Elect of the Cardiac Society Australia and New Zealand Cardiovascular Genetic Diseases Council, and have a close working relationship with members of the group.

I enjoy educating and mentoring students and junior doctors. Currently, I am a mentor in the Flinders University Reflective Professionalism Program and in 2018 worked as the Introduction to Clinical Practice Clinical Coordinator for the second year Medical students. This role involved curriculum development, both small group and lecture based teaching, marking and supporting students as they adjust to longer term practical placements.

EDUCATION AND AWARDS

Doctor of Philosophy	The University of Auckland, New Zealand	2018
Advanced Cardiac Life Support	Auckland, New Zealand	2017
The Green Lane Research and Educational Fund Senior Fellowship	Auckland, New Zealand	2015 (1 year)
The National Heart Foundation Fellowship in Inherited Heart Disease	Auckland, New Zealand	2013 (2 years)
Fellow of the Royal Australasian College of Physicians (Adult Cardiology)	Royal Australasian College of Physicians	2012
Advanced Paediatric Life Support	Australia	2012
Flinders University Research Scholarship	Adelaide, South Australia	2012
2 nd Cardiac MRI Teaching Course and Workshop, Level 1 MRI	Sydney, Australia	2010
BICMed Course (Basic Intensive Care Medicine)	Royal Adelaide Hospital, South Australia	2009
Teaching on the Run Course	Royal Adelaide Hospital, South Australia	2009
Bachelor of Medicine, Bachelor of Surgery	The University of Adelaide, South Australia	2004
Florey Award	The University of Adelaide, South Australia	2004
Recognition of Service to Adelaide Medical Students' Society	The University of Adelaide, South Australia	2004
Adelaide Medical Students' Society Secretary	The University of Adelaide, South Australia	2002
Adelaide University Rural Club Executive	The University of Adelaide, South Australia	2001, 2002
John Flynn Scholarship		2000-2004
Rotary International Youth Exchange (Germany)	Rotary International, Australia	1998
Seymour College	South Australia	1985-1997

GRANTS AWARDED

Green Lane Research and Educational Fund Limited Budget Grant	\$20 000	2016
Green Lane Research and Educational Fund Senior Fellowship	\$100 000	2014
TM Hosking Charitable Trust	\$39 200	2014
CSANZ Summer Studentship	\$5000	2014

PROFESSIONAL MEMBERSHIPS

Royal Australasian College of Physicians

Cardiac Society of Australia and New Zealand

Australian Health Practitioner Regulation Agency (General and Specialist Registration)

PRESENTATIONS

The Association of Inherited Cardiac Conditions, Belfast, Northern Ireland, 2017

Speaker: *The Muscular Masqueraders (Mimickers of Hypertrophic Cardiomyopathy)*

World Congress Pediatric Cardiology and Cardiac Surgery, Barcelona, Spain, 2017

Speaker: *A New Holter Technique to Diagnose and Risk Stratify Children with Long QT Syndrome*

Cardiac Society Australia New Zealand Annual Scientific Meeting New Zealand, Auckland, 2015

Speaker: *How and when to measure the QTc*

Heart Rhythm New Zealand, Auckland, 2014.

Speaker: *Preliminary results – physical and psychological consequences of left cardiac sympathetic denervation for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia.*

Heart Rhythm New Zealand, Tauranga, 2013.

Speaker: *Long QT Syndrome, Research in New Zealand*

Cardiac Society Australia New Zealand Annual Scientific Meetings, Gold Coast and Wellington, 2013.

Speaker: *Sudden Death in the Young, CIDG Case Presentation*

PUBLICATIONS

Waddell-Smith, KE; Chaptynova, AA; Li, J; Crawford, JR; Hinds, H; Skinner, JR. Evaluation of a heart rate-restricted Holter monitor technique in the diagnosis and assessment of long QT syndrome. Under peer review.

Earle, NJ; Crawford, J; Hayes, I; Rees, MI; French, J; Stiles, MK; **Waddell-Smith, KE**; Donoghue, T; Monkley, R; Neas, K; Aitken, A; Tse, R; Love, DR; Skinner, JR. Development of a cardiac inherited disease service and clinical registry: A 15-year perspective. American heart journal. 2018 (in press).

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Camuglia AC, **Waddell-Smith KE**, Hammett CJ, Aylward PE. The potential role of anticoagulant therapy for the secondary prevention of ischemic events post-acute coronary syndrome. *Current Medical Research Opinion*. 2014;30(11):2151-67.

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Waddell-Smith, K. Parsonage, W. Arstall, M. Coverdale, S. Prasad, C. Cross, D. Collins, N. Juergens, C. Prasan, A. Rankin, J. Fitzpatrick, D. Van Gaal, B. Matichoss, S. Horsfall, M. Chew, D. Vaile, J. Under-treatment of Women with Acute Coronary Syndrome Appears to be Related to Unrecognised Risk. *Heart, Lung and Circulation*. 2011;20S:S44.

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Prakash, R. Malkin, C. Chew, D. Horsfall, M. Amerena, J. Markwick, A. Judd, J. **Waddell-Smith, K.** Wong Y. The Impact of Advanced Age on Clinical Outcome from an Early Invasive Strategy in Patients with Acute Coronary Syndrome. The Acute Coronary Syndrome Prospective Audit registry (ACACIA). *Heart, Lung and Circulation*. 2011;20S:S149.

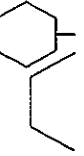
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Wong, Y. Joseph, M. Chew, D. Bennetts, J. Chong, F. Selvanayagam, J. Penhall, A. Horshall, M. Prakash, R. Judd, J. **Waddell-Smith, K.** Markwick, A. Sinhal A. Comparison of Early Haemodynamic Performance Between Transcatheter Aortic Valve Implantation (TAVI) and Surgical Aortic Valve Replacement (SAVR) Bioprosthesis. *Heart, Lung and Circulation*. 2011;20S:S164.

ABSTRACTS

Waddell-Smith, KE; Smith, CM; Mehta, S; Rusk, RA. “A cute” story of laxity. Presented at The Association of Inherited Cardiac Conditions, Belfast, Northern Ireland, 2017.

Waddell-Smith, KE; Li, J; Smith, W; Crawford, J; Skinner JR. Beta-blocker adherence is suboptimal in familial long QT syndrome. Presented at the *Asia Pacific Heart Rhythm Society Scientific Sessions*, Melbourne, Australia, 2015.



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13 March 2019

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Dear Doctor,

Re: Kathleen Megan Folbigg

We advise that we act for Ms Kathleen Megan Folbigg in relation to the special Inquiry ordered into her convictions by the NSW Governor on 22 August 2018.

Report

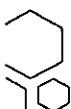
We have been instructed to seek your expert opinion report in relation to the cause of death of Caleb Gibson Folbigg, Patrick Allen Folbigg, Sarah Kathleen Folbigg and Laura Elizabeth Folbigg. I draw your attention to the following Court Rules, copies attached:

1. UCPR 31.23 Code of Conduct;
2. UCPR 31.27 Experts' reports; and
3. UCPR Schedule 7 – Expert witness code of conduct.

Your report should be addressed to me at Cardillo Gray Partners.

In order for the report to be of value in the current proceedings, your report must state:-

1. Your name and address.
2. That you comply with Regulation 31.27,
3. That as an expert, you have specialised knowledge based upon your training, study or experience set out in the report,



4. Sets out the opinion that you hold as an expert, and which is wholly or substantially based upon that specialised knowledge, and
5. Set out your reasons for your opinion, and to the extent that you have relied on any scientific study or other literature, refer to that literature by footnote or bibliography.
6. Attach a copy of this letter, the letter of instruction and its attachments to your report;
7. Complete and attach the Certificate - Expert Report;
8. Complete and attach the Expert Certificate, s 177 Evidence Act

Attached Documents

We have already provided to you the following:

1. Summary of medical evidence on each Folbigg child extracted from a journal article (5 pages);
2. Autopsy report of Caleb Folbigg;
3. Autopsy report of Patrick Folbigg;
4. Autopsy report of Sarah Folbigg;
5. Autopsy report of Laura Folbigg;
6. Cardiology documents provided by the Inquiry (pages 1 - 35);
7. Cardiology documents from the Forensic Pathology Tender Bundle (62 pages);
8. Cardiology documents from the Genetics Tender Bundle (20 pages);
9. Report on Whole Exome Sequencing analysis from Professor de Vinuesa dated 2 December 2018;
10. Report on Whole Exome Sequencing from Professor de Vinuesa dated 7 December 2018; and
11. Letter regarding Whole Exome Sequencing from Professor de Vinuesa dated 18 December 2018.

Questions

In preparing your report we would be pleased if you would address the following questions:

1. What categories, if any, are used to identify the impact of genetic variants on cardiac health?
2. When you are considering the cardiac functioning of a child, do you consider the impact of genetic variants?
3. What emphasis do you place on genetic variants when considering the cardiac health of a child?

4. At what age is ECG reliable in young children?
5. At what age is it usual to employ genetic testing on a child (in a current clinical context)?
6. Any further comments you wish to make.

If any question that we have posed does not make sense to you from the perspective of your specialty, kindly advise us of the issue that it presents and we will attempt to clarify it.

We undertake to be responsible for your professional fee and look forward to conferring with you shortly.


Would you please address your tax invoice as follows:

Kathleen Megan Folbigg
CO/ Cardillo Gray Partners
PO Box 409
Newcastle NSW 2300

Should you have any questions or wish to discuss this matter please do not hesitate to contact us on (02) 4910 0677.

Yours Faithfully
CARDILLO GRAY PARTNERS

Stuart Gray
Partner

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Encl.: